

## REMARKS

**Claim status.** Claims 1 to 7, 10 and 52 are pending in this application. All pending claims stand rejected under 35 U.S.C. Section 103. Claim 1 has been amended hereby.

**Support for Amendments.** The amendment to Claim 1 concerning peptide length is explicitly supported in the specification at page 19, line 28. Further support is found in the remainder of that same paragraph at page 19-20 and at page 3, lines 10-11. The amendment to Claim 1 adding the word "randomized" is supported at page 20, lines 4-10.

**Rejections under Section 103(a).** The Examiner cited three grounds of rejection under Section 103(a):

1. Claims 1 to 6 remain rejected over WO 98/24477 (Bendele *et al.*) or WO 97/28828 (Collins *et al.*), but the Examiner has removed reliance upon WO 99/142/44 (Kohler) as a reference.
2. Claims 1 to 3, 5, 6, 10 and 52 remain rejected over Bendele *et al.* or Collins *et al.* in view of U.S. Pat. No. 5,608,035 (Yanofsky *et al.*), and WO 98/46257 (Brems *et al.*), with reliance on the Kohler reference again removed.
3. In a new ground of rejection, Claims 1-6, 10, and 52 stand rejected over Bendele *et al.* or Collins *et al.* in view of Yanofsky *et al.*, Brems *et al.*, and U.S. Pat. No. 5,336,603 (Capon *et al.*).

In her review of the first ground of rejection under Section 103, the Examiner noted that "the rejected claims have no limitation of the size of the peptide claimed." (Office Action at page 9). In response to this statement and in the interest of compact prosecution, the Applicants hereby add the specification's definition of peptide, specifying length, to Claim 1.

The Yanofsky *et al.* reference concerns peptides that bind to the IL-1 receptor. As noted in the Applicants' response of February 28, 2002, the Yanofsky reference states that its peptides can serve as structural models for non-peptidic compounds (col. 20, lines 61 to 67). Yanofsky *et al.* thus reflect the divergent use of peptides in the art from the present invention, as noted in the Applicants' Background of the Invention (page 10, lines 2 to 13). The Yanofsky reference describes *in vivo* uses, pharmaceutical compositions, dosage, and dosage forms (col. 22, line 11 to col. 24, line 32). The Yanofsky reference, does not, however, recognize the desirability of increasing the half-life of such peptides (*Cf.* specification at page 10, lines 15 to 17; page 17, lines 15 to 25) and does not further suggest accomplishing such increased half-life by linkage to an Fc domain.

Bendele *et al.*, Collins *et al.*, Brems *et al.* and Capon *et al.* refer to natural proteins rather than the randomized peptides of the present claims. The proteins of these references are of significantly greater length than the peptides cited in the present claims and they are identified from natural sources. Thus, they do not suggest use of randomized peptides linked to Fc domains.

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The Examiner alleged that Capon *et al.* disclosed the use of small peptides, citing column 5, line 60 to column 6, line 15, and column 7, lines 10 to 30 of Capon *et al.* The cited text, however, refers only to "the domains of adhesons that are homologous to immunoglobulins and extracellular in their native environment" (col. 5, lines 61-63) and to "at least a portion of the extracellular domain of an adheson containing its ligand binding site" (col. 7, lines 14-15). The specification as a whole shows that this language refers to protein fragments larger than the claimed 2 to 40 aa peptides; see, for example, the adheson sequence that stretches over Figures 1A, 1B-1, 1B-2, and 1C of Capon *et al.* Furthermore, the binding site of HIV on CD4 was found to be outside the claimed 2 to 40 aa peptide length. (See Kuby, *Immunology*, W.H. Freeman and Company, New York, page 461, copy enclosed). Most important, the cited text shows that Capon *et al.* did not contemplate the randomized peptides of the claimed invention: column 7 refers to "the extracellular domain of an adheson" and column 5 refers to the adhesons "in their native environment".

The Examiner further alleged that Capon *et al.* disclosed the use of more than one peptide in tandem. This allegation appears to be based on the list of molecules in col. 7, lines 19-29. When read in context, however, that list describes not tandem repeats of an adheson fragment on a single polypeptide chain but rather dimers and heterodimers of fusion proteins having an adheson fragment linked to a constant region domain. This reading is consistent with the text preceding the list, quoted below:

According to this invention, CD4-IgG immunoadheson chimeras are readily secreted wherein the CD4 epitope is present in heavy chain dimers, light chain monomers or dimers, and heavy and light chain heterotetramers wherein the CD4 epitope is present fused to one or more light or heavy chains, including heterotetramers wherein up to and including all four variable region analogues are derived from CD4. Where light-heavy chain non-CD4 variable domain is present, a heterofunctional antibody thus is provided.

Various exemplary hetero-and chimeric immunoadheson antibodies produced in accordance with this invention are schematically diagrammed below.... (col. 6, line 68 to col. 7, line 13).

The text following the list also makes clear that dimers and heterodimers are intended, particularly the sentence reading, "These examples are representative of divalent antibodies...." (col. 7, lines 38 to 39). When read in context, then, entries (a) and (b), AC<sub>L</sub> and AC<sub>L</sub>-AC<sub>L</sub>, represent the "light chain monomers or dimers" mentioned at col. 7, line 3, quoted above. The remaining entries at lines 19 to 29 similarly represent dimers or heterodimers.

A reading of the list at lines 19 to 29 as tandem repeats on a single chain would, in contrast, be inconsistent with the remainder of the specification. Such an interpretation would mean that not only the adheson fragment but the antibody constant regions and variable regions would also appear in a single chain. That would mean that under

entry (d), Capon *et al.* meant to include  $AC_L-V_H C_H - AC_L-V_H C_H$  (see entry (e)) in a single chain. Nothing in the specification of Capon *et al.* suggests that they contemplated nor taught how to prepare such unwieldy single-chain molecules.

**Conclusion.** In light of the foregoing, the Applicants respectfully request entry of all amendments and allowance of all claims.

Respectfully submitted,

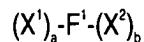


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VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. A composition of matter of the formula



and multimers thereof, wherein:

$F^1$  is an Fc domain;

$X^1$  and  $X^2$  are each independently selected from  $-(L^1)_c - P^1$ ,  $-(L^1)_c - P^1 - (L^2)_d - P^2$ ,  $-(L^1)_c - P^1 - (L^2)_d - P^2 - (L^3)_e - P^3$ , and  $-(L^1)_c - P^1 - (L^2)_d - P^2 - (L^3)_e - P^3 - (L^4)_f - P^4$

$P^1$ ,  $P^2$ ,  $P^3$ , and  $P^4$  are each independently randomized IL-1 antagonist peptide sequences;

$L^1$ ,  $L^2$ ,  $L^3$ , and  $L^4$  are each independently linkers; and

$a$ ,  $b$ ,  $c$ ,  $d$ ,  $e$ , and  $f$  are each independently 0 or 1, provided that at least one of  $a$  and  $b$  is 1  
and wherein "peptide" refers to molecules of 2 to 40 amino acids.

53. The composition of matter of Claim 1, wherein c is 1.

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## HIV Infection of Target Cells

Entry of HIV into target cells involves two steps: binding of virions to receptors on target cells followed by fusion of the viral envelope with the plasma membrane of the target cells. The two glycoproteins—gp120 and gp41—that make up the surface projections on HIV play vital roles in these initial steps in HIV infection. Once inside a target cell, the viral genome is integrated into the host-cell genome, forming a *provirus*, which may remain in a latent state or be activated and transcribed into viral proteins.

### HIV Binding to Cells

The first step in HIV infection is binding of viral gp120 to receptors on target cells. Because the CD4 membrane molecule on the surface of T<sub>H</sub> cells is the principal cellular receptor for HIV, the virus is said to be *lymphotothic*. Other cells (e.g., macrophages, monocytes, dendritic cells, Langerhans' cells, hematopoietic stem cells, certain rectal-lining cells, and microglial cells) also express low levels of CD4 and thus exhibit some binding of HIV. HIV-1 has a 25-fold higher affinity for CD4 than HIV-2. The lower binding ability of HIV-2 may account, in part, for its lower pathogenicity compared to HIV-1. The importance of CD4 in HIV binding has been demonstrated by transferring the gene encoding CD4 into cells in culture (e.g., HeLa cells) that lack CD4; such cells, formerly resistant to HIV, become susceptible to HIV infection after transfection.

The CD4-binding sequence on gp120 was determined by researchers at Genetech, who transfected Chinese Hamster Ovary (CHO) cells with the CD4 gene. They found that soluble, cloned [<sup>125</sup>I] labeled gp120 could bind to these transfected cells but not to untransfected controls. They then cleaved the gp120 molecule into peptide fragments, produced monoclonal antibody to each fragment, and tested the ability of each monoclonal antibody to inhibit binding of the radiolabeled gp120 to the CD4-transfected CHO cells. By using this procedure, they identified a largely conserved region of amino acids (397–439) near the carboxy terminus of gp120 that appeared to be involved in CD4 binding. Further evidence for the role of this sequence in CD4 binding was obtained by synthesizing a peptide with this sequence and showing that it could also block binding of soluble radiolabeled gp120 to the CD4-transfected CHO cells. When regions within the 397–439 sequence were deleted, a substantial reduction in binding to CD4 occurred.

Although the CD4 molecule is the high-affinity receptor for HIV, studies have shown that expression of CD4 by a cell is not always sufficient or necessary for HIV infection. For example, when the gene for CD4 is

transfected into mouse cells, these transfected cells still cannot be infected with HIV even though they express CD4. This finding led to the suggestion that some other membrane molecule or intracellular event must be necessary for viral entry into cells. On the other hand, some cells that lack detectable CD4 can be infected with HIV, although it is not known how the virus enters these cells. For instance, HIV has been shown to infect some brain-derived cell lines that lack CD4, and to do so even in the presence of excess soluble CD4. These findings led some researchers at the VI International AIDS Conference in 1990 to propose that a membrane molecule other than CD4 may serve as a universal receptor for HIV, allowing the virus to bind to cells lacking CD4. These various results suggest that in some cases HIV can enter cells by some mechanism other than binding of gp120 to CD4.

### Fusion of HIV with Cells

After binding of HIV to its receptor (principally CD4), the viral envelope fuses with the target-cell plasma membrane. The fusion event appears to be induced by a hydrophobic region near the amino terminus of gp41; this region is called the *fusogenic domain*. Following fusion, the HIV nucleocapsid is internalized, and the viral RNA is uncoated, establishing a productive infection (Figure 21-3a, steps 1–4).

### HIV Replicative Cycle

Once the HIV RNA has been introduced into a target cell and uncoated, it is transcribed into DNA by the viral reverse transcriptase enzyme. The viral DNA is integrated into the host-cell genome, forming a provirus, which can remain in a latent state and be passed on to daughter cells. Activation of the provirus initiates transcription of the structural genes into mRNA, which is translated into viral proteins. The host plasma membrane is modified by insertion of gp41 and associated gp120; the viral RNA and capsid protein then assemble beneath the modified membrane, acquiring the modified host plasma membrane as its envelope in a process called *budding*. In some cases the process of budding goes on at a low level, allowing the infected cell to survive; in other cases the assembly of viral particles and budding is so massive that the host cell is lysed (see Figure 21-3b–d). The infection of macrophages and monocytes generally does not lead to cell death, and there is some speculation that HIV-bearing macrophages may serve as a major reservoir of HIV, carrying it to various organs and even across the blood-brain barrier.